PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 05-102NIQ	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2005/002743	International filing date *(day/month/year)* 21 February 2005 (21.02.2005)	Priority date *(day/month/year)* 20 February 2004 (20.02.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 September 2006 (19.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference 05-102NIQ	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/002743	21.02.2005	20.02.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant

NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP Facsimile No.	Authorized officer Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/002743

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☒ in computer readable form

c. time of filing/furnishing

☒ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:

   ☐ paid additional fees

   ☐ paid additional fees under protest

   ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

The inventions of claims 1-8 concern DNA or RNA modified at the terminus by a peptide via a bifunctional linker having the specific chemical structure represented by the Formula in claim 1.

Conversely, the siRNA inventions of claims 9-13 are specified by the fact that a chemical modification group is inserted therein, but they do not state that this chemical modification group has the aforementioned specific chemical structure.

Therefore, this authority finds that both groups of inventions do not constitute one group of inventions so linked as to form a single general inventive concept.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. _____

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/002743

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5-13	YES
	Claims	1-4	NO
Inventive step (IS)	Claims		YES
	Claims	1-13	NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims		NO

2. Citations and explanations:

Document 1: JP 2004-275140 A (National Institute of Advanced Industrial Science and Technology) 07 October 2004
Document 2: Kosuke MARUYAMA et al., DNA Conjugate no Saiboshitsu Kyokuzaika, Kagaku Kanren Shibu Godo Kyushu Taikai Koen Yokoshu, 5 July 2003, Vol. 40th, page 146, upper part
Document 3: Kotomi SASAKI et al., DNA Conjugate o Riyo suru PCR Hanno to Kakunai Delivery, Kagaku Kanren Shibu Godo Kyushu Taikai Koen Yokoshu, 05 July 2003, Vol. 40th, page 146, lower part
Document 4: KUBO T. et al., A novel approach for the solid phase synthesis of DNA-peptide conjugates, Nucleosides, Nucleotides & Nucleic Acids, 2001, Vol. 20, No. 4-7, pages 1321-1324
Document 5: KUBO T. et al., Synthesis of DNA-peptide conjugates by solid-phase fragment condensation, Org. Lett., 24 July 2003, Vol. 5, No. 15, pages 2623-2626
Document 6: KUBO T. et al., Conjugate DNAzymes, Nucleic Acids Resarch Supplement, 2003, No. 3, pages 177-178
Document 7: KUBO T. et al., Antisense effects of DNA-peptide conjugates, Nucleic Acids Research Supplement, 2003, No. 3, p. 179-180
Document 8: KUBO T. et al., Control of intracellular delivery and inhibition of genetic expression by DNA-peptide conjugates, Nucleic Acids Research Supplement, 2003, No. 3, pages 237-238

(Continued in supplemental box)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/002743

Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/year)	Filing date (day/*month*/year)	Priority date (valid claim) (day/month/*year*)
JP 2005-27569 A [E, X]	03.02.2005	04.07.2003	

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/*year*)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.

Claims 1-4

Document 1, which is described in paragraph 0009 of the specification of this application and is a previous application by the applicant and inventors of this application, describes a DNA or RNA conjugate wherein a DNA or RNA fragment is condensed onto a solid carrier with a functional organic compound having an active hydrogen-containing group via a bifunctional linker.

As the applicant also states in paragraph 0009 of the specification of this application, document 1 neither discloses or suggests that the aforementioned DNA or RNA conjugate is localized in the cytoplasm.

However, cytoplasmic localization is a function that the DNA or RNA conjugate originally possessed as a result of its chemical structure, and because this was merely a matter that was heretofore undiscovered, the inventive chemical substance itself is indistinguishable thereby.

Therefore, document 1 describes the inventions of claims 1-4 of this application, and these inventions lack novelty.

Claims 5-13

The technical content of document 1 has been described above.

Although not described in the specification of this application, document 2, which was written by the inventors of this application, describes that when a conjugate of a nuclear export signal (NES) peptide and an oligonucleotide was synthesized by the solid phase fragment condensation method and testing of rational control of intracellular delivery and cytoplasmic localization was performed, insertion into the cell of the DNA-NES conjugate and cytoplasmic localization thereof were confirmed thereby.

In addition, although not described in the specification of this application, document 3, which was written by the inventors of this application and is located on the bottom of the same page as document 2, describes the synthesis of an oligonucleotide conjugated with an amine and peptide at the 5' terminus by the solid phase fragment condensation method with the goal of developing a nonviral vector for gene therapy wherein a cellular insertion agent such as a cationic liposome and the like is not needed, insertion into a cell can be performed efficiently, and delivery into the cell can be precisely controlled. Document 3 also states that testing of intracellular insertion efficiency and intracellular localization was performed.

Document 4 was written by the inventors, and although not described in the specification of this application, it is presented in document 3 as a prior art document describing the aforementioned solid phase fragment condensation method. Thus, document 4 describes in detail the solid phase fragment condensation method for preparing a DNA-peptide conjugate. In addition, document 5, which was written by the applicant and inventors of this application and is described in paragraph 0009 of the specification of this application describes in detail the solid phase fragment condensation method for preparing a DNA-peptide conjugate.

(Continued)

Supplemental Box

Continuation of: Box V.

Although not described in the specification of this application, document 6, which was written by the inventors of this application, states that the oligonucleotide conjugated with an amine and peptide at the 5' terminus by the solid phase fragment condensation method presented in document 4 (DNAzyme) above not only increases affinity toward a target RNA and stability against degradation by DNAase, but also has greater activity than the original DNAzyme, and inhibits BCL-ABL tyrosine kinase. In addition, it suggests that the conjugate can be expected to function effectively *in vivo*.

Document 7, which was also written by the inventors of this application and was published in the same publication as document 6, discloses that antisense DNA wherein a nuclear export signal (NES) peptide is conjugated to the 5' terminus by the solid phase fragment condensation method presented in document 4 above was found to have higher telomerase inhibitory activity than original the antisense DNA. In addition, it discloses that increase of the stability against degradation by DNAase, and in particular the conjugate formed by the NES of HIV-1 Rev is localized in the cytoplasm.

Document 8, which was also written by the inventors of this application and was published in the same publication as documents 6 and 7 states that an oligonucleotide conjugated with a nuclear export signal (NES) peptide on the 5' terminus by the solid phase fragment condensation method presented in document 4 above (DNAzyme) is localized in the cytoplasm unlike one that is conjugated with a nuclear localization signal (NLS) peptide, and it has higher BCL-ABL tyrosine kinase inhibitory activity than the original DNAzyme.

Therefore, in light of the descriptions of publicly known documents 1-8, which were all written by the inventors of this application, this authority finds that persons skilled in the art could easily conceive of each of the inventions of claims 5-13 of this application.